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Long-term endurance and safety of elosulfase alfa enzyme replacement therapy in patients with Morquio A syndrome

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ABSTRACT

Long-term efficacy and safety of elosulfase alfa enzyme replacement therapy were evaluated in Morquio A patients over 96 weeks (reaching 120 weeks in total from pre-treatment baseline) in an open-label, multicenter, phase III extension study. During this extension of a 24-week placebo-controlled phase III study, all patients initially received 2.0 mg/kg elosulfase alfa either weekly or every other week, prior to establishment of 2.0 mg/kg/week as the recommended dose, at which point all patients received weekly treatment. Efficacy measures were compared to baseline of the initial 24-week study, enabling analyses of changes over 120 weeks. In addition to performing analyses for the entire intent-to-treat (ITT) population ($N = 173$), analyses were also performed for a modified per-protocol (MPP) population ($N = 124$), which excluded patients who had orthopedic surgery during the extension study or were non-compliant with the study protocol (as determined by ≥20% missed infusions). Six-minute walk test (6MWT) was the primary efficacy measure; three-minute stair climb test (3MSCT) and normalized urine keratan sulfate (uKS) were secondary efficacy measures. Mean (SE) change from baseline to Week 120 in 6MWT distance was 32.0 (11.3) m and 39.9 (10.1) m for patients receiving elosulfase alfa at 2.0 mg/kg/week throughout the study ($N = 56$) and 15.1 (7.1) m and 31.7 (6.8) m in all patients combined, regardless of dosing regimen, for the ITT and MPP populations, respectively. Further analyses revealed that durability of 6MWT improvements was not impacted by baseline 6MWT distance, use of a walking aid, or age. Mean (SE) change at Week 120 in the 3MSCT was 5.5 (1.9) and 6.7 (2.0) stairs/min for patients receiving elosulfase alfa at 2.0 mg/kg/week throughout the study and 4.3 (1.2) and 6.8 (1.3) stairs/min in all patients combined, regardless of dosing regimen, for the ITT and MPP populations, respectively Across all patients, mean (SE) change at Week 120 in normalized uKS was −59.4 (1.8)% and −62.3 (1.8)% in the ITT and MPP

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test; AE, adverse event; ERT, enzyme replacement therapy; GALNS, enzyme *N*-acetylgalactosamine-6-sulfatase; IAR, infusion-associated reaction; IgE, immunoglobulin E; ITT, intent-to-treat; KS, keratan sulfate; MPP, modified per-protocol; MorCAP, Morquio A Clinical Assessment Program; NAb, neutralizing antibody; PBO, placebo; QOW, every other week; QW, once weekly; SAE, serious adverse event; TAb, total antibody; uKS, urine keratan sulfate.

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populations, respectively. In the absence of a placebo group, significance of the sustained improvements could not be evaluated directly. However, to provide context for interpretation of results, comparisons were performed with untreated patients from a Morquio A natural history study. In contrast to the results of the extension study, the untreated patients experienced constant uKS levels and a gradual decline in endurance test results over a similar period of time. Differences from the untreated natural history study patients were significant for 6MWT, 3MSCT, and uKS outcomes for the cohort of patients receiving optimal dosing throughout the study and for all cohorts pooled together, for both ITT and MPP populations ($P < 0.05$). Safety findings were consistent with those of the initial 24-week study, with no new safety signals identified.

1. Introduction

Morquio A syndrome (mucopolysaccharidosis IVA) is a rare autosomal recessive disorder caused by mutations in the lysosomal enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS, EC 3.1.6.4). Reduced GALNS enzyme activity results in progressive accumulation of chondroitin-6-sulfate and keratan sulfate (KS) in tissues and organs, leading to dysfunctions in multiple organ systems [1–3]. Due to the rarity of Morquio A syndrome and variations in reporting methods used, accurate prevalence and incidence estimates have not yet been established, with reported birth prevalence ranging widely from 1 in 71,000 to 1,179,000 [4].

Characteristic features of Morquio A include skeletal and joint abnormalities, short stature, cardiorespiratory compromise, nerve entrapment syndromes, impaired vision, hearing loss, and hepatomegaly [1–3]. There is a wide heterogeneity among patients in genotype, clinical presentation, and progression rate. However, regardless of an individual's presentation of the disease, over time, the progressive nature of symptoms ultimately results in deteriorating mobility and endurance, limitations in performing the activities of daily life, and early mortality [5,6].

Enzyme replacement therapy (ERT) with recombinant human GALNS (elosulfase alfa, Vimizim®, BioMarin Pharmaceutical Inc., Novato, CA) has recently been approved as a treatment option for Morquio A [7]. The pivotal 24-week, randomized, placebo-controlled, phase III study showed significant improvements with weekly elosulfase alfa infusions (2.0 mg/kg) on the primary efficacy measure, i.e. distance walked in the 6MWT [8]. After 24 weeks of treatment, 6MWT distance increased by 22.5 m versus placebo ($P = 0.017$). No effect was seen with elosulfase alfa administered every other week. In addition, the study demonstrated non-statistical increases in the 3MSCT and pulmonary function tests versus placebo [8,9]. Normalized urine KS (uKS) was reduced at 24 weeks with both treatment regimens. Long-term safety and efficacy data from an extension of this pivotal study are reported in this manuscript.

2. Methods

2.1. Study design

The study (MOR-005, #NCT01415427) was a multi-national, multicenter, open-label extension of a randomized, double-blind, placebo-controlled, 24-week, phase III study (MOR-004, #NTC01275066) of 176 Morquio A patients [8,9]. The inclusion and exclusion criteria and study design have been published previously [8,9] and included requirements that patients were ≥5 years of age, had a baseline average 6MWT distance ≥30 and ≤325 m at baseline, and did not have major surgery within the 3 months prior to MOR-004 entry. For consistency, both MOR-004 and MOR-005 protocols mandated uniform walking aid use during endurance tests from baseline through last visit. All patients completing MOR-004 were eligible for enrollment in MOR-005. Before entering MOR-005, all participants, and/or their legally authorized representative (as required), provided written informed consent.

In part 1 of MOR-005, patients initially randomized to elosulfase alfa remained on their assigned dosing regimen of 2.0 mg/kg/week (QW-QW cohort) or 2.0 mg/kg/every other week (QOW-QOW cohort); placebo-treated patients were re-randomized (1:1) to one of the two dosing regimens (Fig. 1). Unlike randomization at initiation of MOR-004, re-randomization was not stratified by age or baseline 6MWT. After review of final efficacy and safety results from MOR-004 by an independent data monitoring committee, the recommended dose was established as 2.0 mg/kg/week. As pre-specified in the protocol, all patients were switched to the recommended dose for part 2 of study. Specific study week of transition depended on study enrollment timing and ranged from MOR-004/005 Week 36 to 96.

Although surgeries were not allowed during MOR-004, due to the long-term nature of the extension study, they could not reasonably be prohibited during MOR-005. However, endurance test results can be impacted by the occurrence of orthopedic surgery and the subsequent recovery period. Therefore, the per-protocol population for analysis excluded data on or after orthopedic surgery, as well as 24 week intervals of data where ≥3 infusions were missed and all data subsequent to such intervals. However, at a meeting on February 9, 2015 in Orlando, FL, USA, study investigators determined that the pre-specified per-protocol population was unnecessarily restricted and excluded too many patients (95 patients excluded; 51 patients due to missing ≥3 infusions) and established the modified per-protocol (MPP) population. The MPP population excluded patients who underwent orthopedic surgery during the study ($N = 38$) and/or exhibited recurrent non-compliance with the study protocol. Missed infusions were used as an indicator of compliance; patients missing ≥20% of their scheduled elosulfase alfa infusions during MOR-005 were identified as non-compliant ($N = 14$). In total, 49 patients were excluded, thereby allowing inclusion of an additional 46 patients as compared to the per-protocol population. To reveal the impact of orthopedic surgeries and lack of compliance on endurance, MPP population results are presented alongside results from the entire intent-to-treat (ITT) population (all patients who were previously included in the 24-week phase III study and received at least one dose of elosulfase alfa).

2.2. Efficacy evaluation

The primary efficacy variable of this extension study was distance walked in a 6MWT, which provides a measure for endurance. The 3MSCT, also a measure of endurance, and normalized uKS were secondary efficacy variables. The uKS measurements were normalized by dividing by urine creatinine levels, resulting in μg/mg creatinine units.

In part 1 of MOR-005, the 6MWT and the 3MSCT were performed at Week 12 and Week 24, and at 24-week intervals thereafter. Normalized uKS was assessed every 12 weeks. In part 2 of MOR-005, the 6MWT

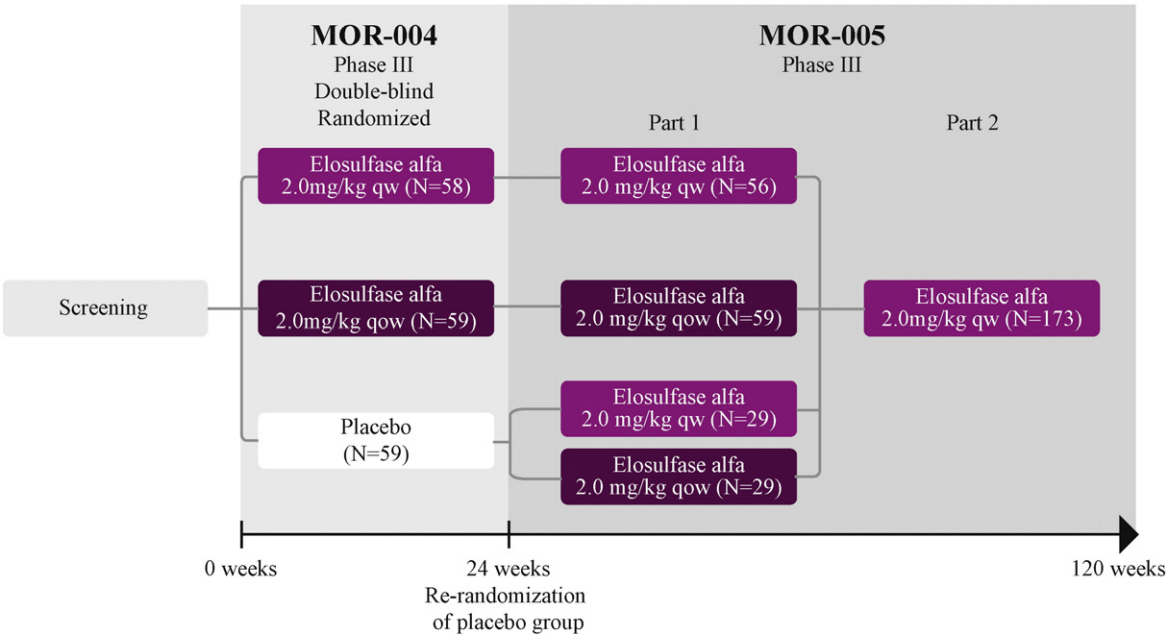

Fig. 1. Study design.

and 3MSCT were performed at 48-week intervals; normalized uKS was assessed every 24 weeks. Endurance tests were performed in duplicate (on separate days) and the average of the two measurements was used as the score for that week. Patients who were physically unable to perform the endurance tests were scored as zero m or stairs/min.

As continuing invasive weekly infusions in the absence of treatment for the duration of this long-term extension study for this rare disorder was considered unethical, a placebo group was not included. In the absence of a placebo group, a direct evaluation of treatment efficacy could not be made. However, to provide context for interpretation of results, comparisons were performed with an untreated population from the Morquio A Clinical Assessment Program (MorCAP) natural history study (MOR-001, #NCT00787995). The study design of MorCAP has been published previously [2,10]. Briefly, MorCAP was a multinational, multi-center, cross-sectional study, later amended to be longitudinal. Visits were conducted annually with each visit including collection of medical history, clinical assessments, and uKS measurement. The subset of MorCAP patients meeting the following criteria: ≥5 years of age and average 6MWT distance ≥30 and ≤325 m at baseline, for whom longitudinal data (Year 1 and/or Year 2 follow-up) were available, were used to establish an untreated subpopulation (MorCAP 1) comparable to the MOR-005 ITT population. MorCAP 1 was further restricted to exclude patients who underwent orthopedic surgery within the 3 months prior to the time at which their baseline data were collected or during the subsequent 2 year period to establish an untreated subpopulation (MorCAP 2) comparable to the MOR-005 MPP population.

2.3. Safety evaluation

Safety in MOR-005 was assessed by examining incidence, severity, and relationship of elosulfase alfa to treatment-emergent adverse events (AEs). Vital signs were measured just before, during, and immediately after the infusion and at least 60 min post-infusion. AEs and concomitant medications were recorded throughout the study and reviewed every 4 months by an independent data monitoring committee. The following safety parameters were assessed every 12 weeks during part 1 and then at 24-week intervals during part 2 of MOR-005: infusion-associated reactions (IARs), standard clinical laboratory results, physical examination, immunogenicity, and pregnancy testing (as appropriate). IARs were defined as any AE (regardless of drug relationship) occurring after infusion onset and within 1 day post infusion. Routine immunogenicity testing included assays for anti-elosulfase alfa total antibody (TAb), neutralizing antibody (NAb, a subset of TAb that inhibit receptor binding), anti-elosulfase alfa immunoglobulin E (IgE), and total IgE (baseline only). Immunogenicity tests were performed using validated immunogenicity assays on blood samples as described previously [11]. Samples were collected prior to study drug infusion at baseline and at Weeks 2, 4, 8, 12, 16, 20, and 24 during MOR-004, every 12 weeks in MOR-005 part 1, and every 24 weeks in MOR-005 part 2. TAb titers were determined by a bridging electrochemiluminescence assay that measures multiple anti-drug antibody isotypes in a single assay. TAb-positive samples were confirmed for specificity against elosulfase alfa and serially diluted to obtain a titer. A qualitative NAb assay was used to determine whether patient TAb could neutralize binding of biotin-labeled elosulfase alfa to CI-M6PR immobilized on an ELISA plate. When TAb was negative, NAb was not assessed. Anti–elosulfase alfa IgE was detected by a sandwich radioimmunoassay. Elosulfase alfa specificity was confirmed for samples that screened positive for anti-drug IgE and results were reported as positive or negative. Subjects with a severe IAR or IAR requiring infusion cessation had an additional blood sample taken to assess total IgE, drug specific IgE levels, complement, and tryptase. Potential hypersensitivity AEs were identified by utilizing the broad Anaphylactic Reaction algorithmic Standardized Medical Dictionary of Regulatory Activities (MedDRA) query (SMQ) (MedDRA, version 15.0, http://www.meddra.org/) and the broad Angioedema SMQ.

2.4. Statistical methods

The analyzed data were collected during both the initial 24-week study and 96 weeks of the extension study, representing a total of 120 weeks. Descriptive statistics of efficacy endpoints are provided for both the ITT and MPP populations. A repeated measures ANCOVA model including treatment, time point, treatment and time point

interaction, baseline age stratification (5–11, 12–18, ≥19 years), baseline 6MWT distance stratification (≤200 m and >200 m), and baseline measurement (for 3MSCT and uKS) as factors was used for the comparison of least squares mean (LS mean) changes from baseline at Year 1 and Year 2 between MOR-005 and MorCAP populations. Of the four treatment cohorts, only the QW-QW cohort was directly compared to MorCAP due to complications with assessment timing alignment (PBO-QW, PBO-QOW) and/or variable dosing (PBO-QOW, QOW-QOW) for the remaining cohorts. To reduce the impact of these complications, while still evaluating all available data, a general evaluation of long-term (96 to 120 week) elosulfase alfa treatment, regardless of dosing regimen, was performed by comparing MorCAP 1 and 2 with pooled data from the combined cohorts for both the ITT and MPP populations, respectively.

The safety analysis included all patients that received any dose of study drug and had any post-treatment safety information. The incidence rates for AEs were summarized by System Organ Class, Preferred Term, relationship to study drug, and severity for each treatment group.

3. Results

3.1. Patient characteristics

Of the 176 patients enrolled in MOR-004, 175 completed MOR-004 (one patient withdrew after a single infusion) and 173 continued into MOR-005 (two patients declined to provide informed consent for MOR-005). One patient in the elosulfase alfa weekly dosing group withdrew consent after completing week 0 of part 1. During part 2 of MOR-005, 16 patients discontinued study drug with the majority of the discontinuations being due to early transition to commercial drug and approximately half occurring after 72 weeks. Two patients enrolled in MOR-005 have not completed the study as they are waiting for an infusion center to open nearer their place of residence.

Of the 353 patients in MorCAP, longitudinal data were available for 184. Of those subjects, 87 did not meet MOR-004/005 inclusion criteria (28 were <5 years of age, 27 walked <30 m at baseline, and 32 walked >325 m at baseline) and were excluded. Therefore, 97 untreated patients were used for comparison with the MOR-005 ITT population. For comparison with the MOR-005 MPP population, 18 additional MorCAP patients who had orthopedic surgery between 3 months prior to baseline measurement collection and 2 years of follow-up were excluded. The incidence of surgeries was similar between MOR-004/005 (38/173, 22%) and MorCAP (18/97, 19%) patients.

Due to the observational nature of the natural history study, the exact time of follow-up visits varied. Visit windows were 270 through 609 days for the Year 1 assessment and 610 through 944 days for the Year 2 assessment. Mean (SD) actual visit times were 446 (74) and 749 (79) days, or approximately 64 and 107 weeks, for Year 1 and 2, respectively. These times were compared with MOR-004/005 72 and 120 week time points.

Table 1 shows demographics and characteristics for patients enrolled in MOR-005 as well as the corresponding subpopulations of Morquio A patients from the MorCAP natural history study. Baseline demographics and characteristics were relatively similar. Because the number of MorCAP patients was substantially reduced at each time point, baseline characteristics for the patients providing data at each follow-up visit were examined. Despite the smaller samples sizes, baseline characteristics remained similar (Appendix A).

Due to the transition to weekly dosing occurring at a specific date when the recommended dose was established versus at a prespecified study visit, patients receiving QOW dosing were switched to QW dosing at MOR-004/005 Week 36 (39% of patients), Week 48

Table 1
Demographics and MOR-004 baseline characteristics of patients who entered MOR-005 and of the corresponding subpopulations of untreated patients from the MorCAP natural history study.

	ITT						MPP		
	Total N = 173	PBO-QOW N = 29	PBO-QW N = 29	QOW-QOW N = 59	QW-QW N = 56	MorCAP 1 N = 97	Total N = 124	QW-QW N = 43	MorCAP 2 N = 79
Age, yrs									
Mean ± SD	14.4 ± 10.2	16.7 ± 13.7	13.5 ± 8.5	15.3 ± 10.8	12.8 ± 8.0	16.3 ± 12.2	15.4 ± 10.3	13.5 ± 8.6	17.8 ± 13.0
Median	11.7	11.1	11.9	12.0	10.6	11.0	12.2	11.1	12.0
Min, Max	5.0, 57.4	5.0, 57.4	5.0, 33.2	5.0, 49.1	5.0, 41.9	5.0, 65.0	5.0, 49.1	5.0, 41.9	5.0, 65.0
Gender, N (%)									
Female	87 (50.3)	14 (48.3)	18 (62.1)	25 (42.4)	30 (53.6)	56 (57.7)	58 (46.8)	22 (51.2)	48 (60.8)
Male	86 (49.7)	15 (51.7)	11 (37.9)	34 (57.6)	26 (46.4)	41 (42.3)	66 (53.2)	21 (48.8)	31 (39.2)
Ethnicity, N (%)									
White	113 (65.3)	25 (86.2)	18 (62.1)	35 (59.3)	35 (62.5)	86 (88.7)	84 (67.7)	28 (65.1)	72 (91.1)
Non-white	60 (34.7)	4 (13.8)	11 (37.9)	24 (40.7)	21 (37.5)	11 (11.3)	40 (32.3)	15 (34.9)	7 (8.9)
6MWT, m									
Mean ± SD	209.5 ± 74.0	219.7 ± 74.2	207.2 ± 64.9	205.7 ± 81.2	209.4 ± 71.8	207.8 ± 84.3	201.6 ± 74.9	208.8 ± 73.2	210.4 ± 83.4
Median	220.4	239.5	217.2	218.0	218.7	220.5	210.6	226.9	221.5
Min, Max	36.2, 321.5	36.2, 309.9	93.0, 312.2	47.1, 319.6	56.3, 321.5	30.0, 325.0	36.2, 319.6	56.3, 309.0	30.0, 325.0
3MSCT[a], stairs/min									
Mean ± SD	29.1 ± 15.4	33.1 ± 15.6	26.9 ± 12.1	27.1 ± 15.8	30.1 ± 16.2	31.3 ± 17.5	28.7 ± 14.9	31.3 ± 16.2	32.2 ± 17.8
Median	29.2	33.0	29.0	25.5	30.7	29.3	29.6	31.3	30.6
Min, Max	0.0, 71.9	0.0, 59.0	0.0, 50.0	0.0, 66.8	0.0, 71.9	0.0, 85.6	0.0, 71.9	0.0, 71.9	0.0, 85.6
uKS[b,c], μg/mg									
Mean ± SD	27.2 ± 17.2	22.7 ± 15.3	28.5 ± 14.9	28.6 ± 21.2	27.2 ± 14.2	33.5 ± 25.6	25.5 ± 17.6	24.9 ± 13.1	32.2 ± 27.4
Median	26.6	25.0	30.3	27.4	25.0	30.7	23.4	23.4	27.6
Min, Max	2.1, 117.3	3.1, 50.5	2.5, 52.8	2.4, 117.3	2.1, 59.0	2.3, 168.1	2.1, 117.3	2.1, 52.8	2.3, 168.1

Table includes patients who entered MOR-005 using baseline values from MOR-004.
PBO-QOW: Placebo-elosulfase alfa 2.0 mg/kg/qow; PBO-QW: Placebo-elosulfase alfa 2.0 mg/kg/week;
QOW-QOW: elosulfase alfa 2.0 mg/kg/qow-elosulfase alfa 2.0 mg/kg/qow; QW-QW: elosulfase alfa 2.0 mg/kg/week -elosulfase alfa 2.0 mg/kg/week; 3MSCT: 3-min stair climb test; 6MWT: 6-minute walk test; SD: standard deviation.

[a] N = 88 in MorCAP 1 and *N* = 74 in MorCAP 2.

[b] N = 28 in the PBO-QOW cohort, *N* = 172 in the total ITT group and *N* = 123 in the MPP group for urine keratin sulfate (uKS).

[c] uKS is calculated as urine keratan sulfate divided by urine creatinine.

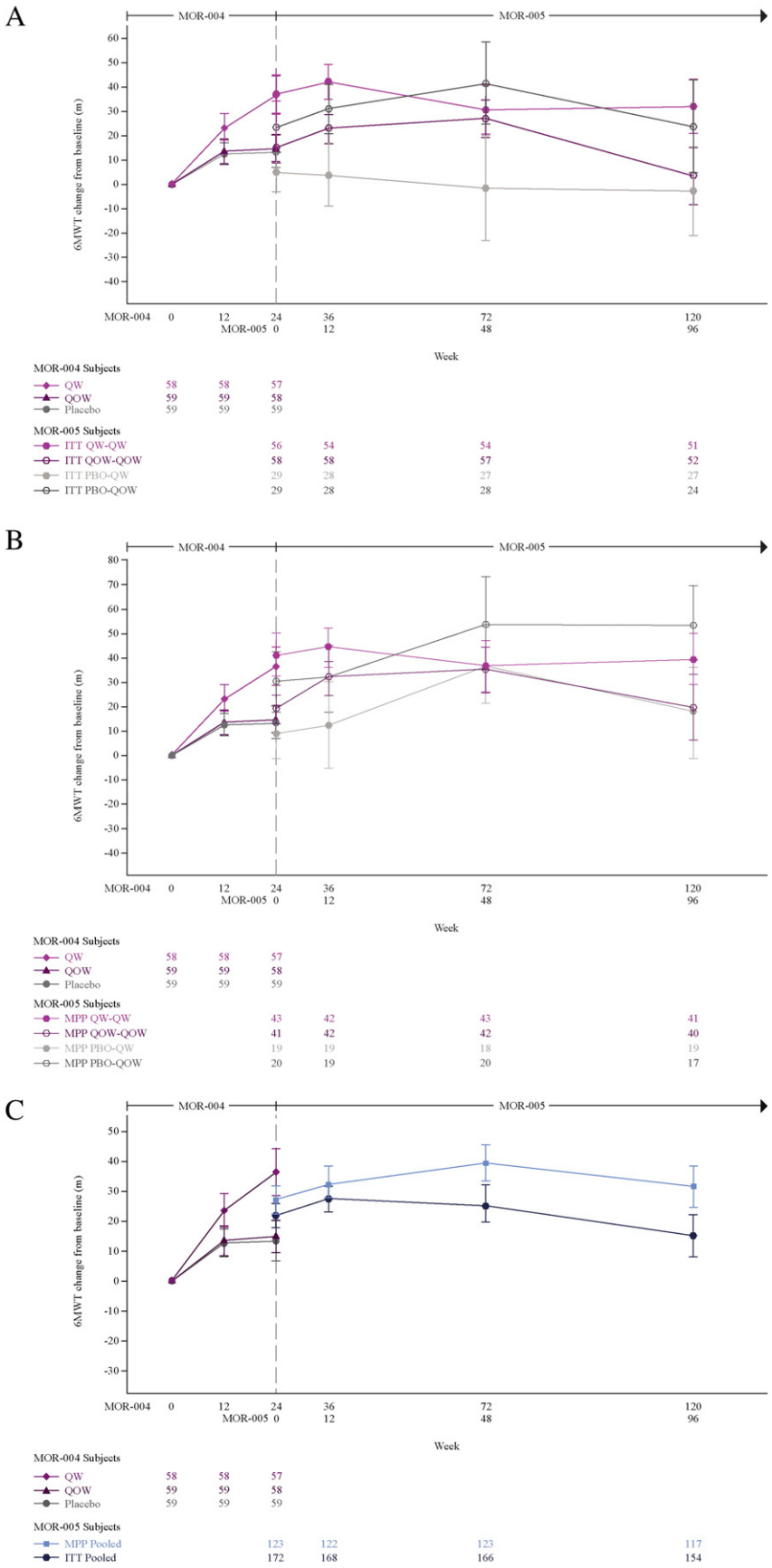

Fig. 2. Mean (SE) change from baseline in 6MWT distance over 120 weeks for treatment cohorts individually (A, B) and pooled (C) for ITT and MPP populations. Not all patients reported results for all time points (including MOR-005 Week 0); the number of patients with data available are shown below each time point.

(43% of patients), Week 72 (16% of patients), and Week 96 (1% of patients). Additionally, Week 48 endurance assessments were performed only for subjects who reached Week 48 while in part 1 of the study as there was no Week 48 assessment in part 2. This led to a greatly reduced sample size at Week 48; therefore, this visit has been omitted from the endurance analyses.

3.2. Primary efficacy variable: 6MWT

In the ITT population, for patients treated for 120 weeks with the optimal dosing regimen (QW-QW), the mean (SE) change in 6MWT distance from pre-treatment baseline was 37.2 (7.9) m at 24 weeks, 42.2 (7.1) m at 36 weeks, 30.7 (10.2) m at 72 weeks, and 32.0 (11.3) m at 120 weeks (Fig. 2A). ITT population results from the remaining treatment cohorts did not indicate consistent improvements similar to those seen in the QW-QW cohort (Fig. 2A). Notably, randomization of the placebo (PBO) group to QW and QOW treatment was not stratified by age or baseline endurance and resulted in unbalanced groups.

Evaluating the MPP population, which excluded non-compliant patients and those who underwent orthopedic surgery, reduced the overall variability of outcomes (Fig. 2B). Mean (SE) changes from baseline for the QW-QW cohort were slightly higher: 41.5 (9.1), 44.4 (8.3), 37.5 (11.0), and 39.9 (10.1) m at 24, 36, 72, and 120 weeks, respectively. Outcomes for the PBO-QOW and PBO-QW groups were also more consistent. Although the mean for the PBO-QOW group had increased more than the PBO-QW group in the absence of treatment, both PBO-QW and PBO-QOW groups showed similar rates of improvement following initiation of treatment. Unfortunately, the staggered transition of QOW-QOW patients to QW treatment precludes meaningful analysis of QOW dosing efficacy. However, an analysis of all cohorts pooled was performed to evaluate the effect of long-term (96 to 120 weeks) elosulfase alfa treatment, regardless of dosing regimen (Fig. 2C). Mean (SE) change from baseline in 6MWT distance was 22.0 (3.9), 27.4 (4.3), 26.1 (6.2), and 15.1 (7.1) m and 27.3 (4.7), 33.2 (5.2), 39.6 (6.2), and 31.7 (6.8) m at 24, 36, 72, and 120 weeks for the pooled cohort ITT and MPP populations, respectively.

Assuming similar timing of approximately 1 and 2 years follow-up in MorCAP and MOR-004/005, model-based ANCOVA analysis demonstrates a significant difference in change from baseline for treated versus untreated patients, for both the QW-QW cohort and the pooled study population (ITT and MPP) (Fig. 3, Table 2).

Sub analyses of the 6MWT data were performed on the MPP population of the QW-QW cohort to facilitate interpretation of the data in the absence of potentially confounding factors (orthopedic surgeries and extensive missed treatments/sub-optimal dosing) (Appendix B). Although patients who used a walking aid (crutches, walker/walking frame, or cane/walking stick) during the 6MWT began the extension study with higher mean improvements in 6MWT distances than those who did not, both groups maintained their initial improvements throughout the study (Appendix Fig. B1). Similarly, patients who had substantially limited baseline endurance (≤200 m 6MWT results) began the extension study with higher mean improvements in 6MWT

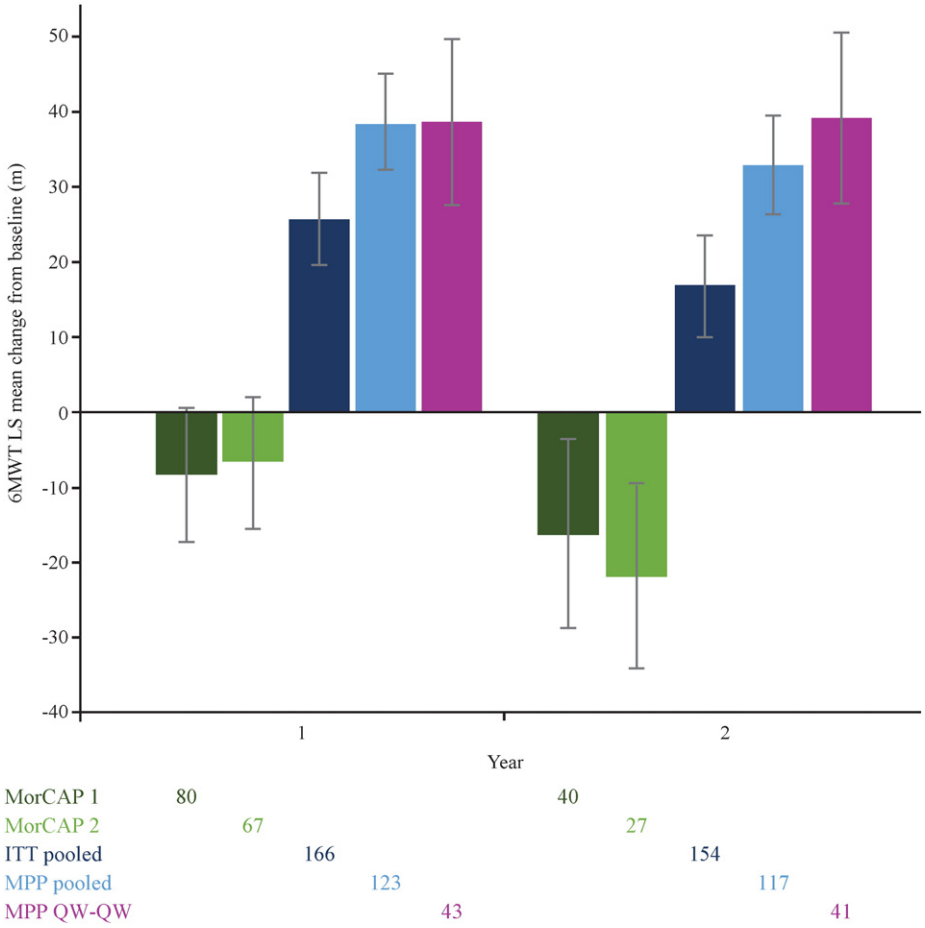

Fig. 3. LS mean 6MWT changes from baseline (m) over approximately 2 years in MOR-004/005 QW-QW and pooled ITT and MPP populations and the corresponding untreated subpopulations from the MorCAP natural history study, MorCAP 1 and 2, respectively. The number of patients with data available are shown below each time point. LS mean changes are based on repeated measures ANCOVA model including treatment, time point, treatment and time point interaction, age group, and baseline 6MWT category.

Table 2
LS mean change from baseline results for 6MWT, 3MSCT, and uKS and comparison with data from the corresponding untreated patients from the MorCAP natural history study.

	Year 1[a]			Year 2[b]		
	MorCAP	MOR-004/005 QW-QW	MOR-004/005 Pooled	MorCAP	MOR-004/005 QW-QW	MOR-004/005 Pooled
ITT Population/MorCAP 1						
6MWT (m)						
N	80	54	166	40	51	154
LS mean change from baseline[c] (SE)[d]	-8.4 (8.91)	31.8 (10.86)	25.5 (6.17)	-16.4 (12.50)	32.1 (11.75)	16.8 (6.72)
P-value[e] for difference from MorCAP		**0.0046**	**0.0019**		**0.0050**	**0.0198**
3MSCT (stairs/min)						
N	80	54	164	40	51	154
LS mean change from baseline[c] (SE)[d]	-0.7 (1.46)	5.0 (1.71)	5.1 (0.98)	-1.1 (2.27)	5.3 (2.10)	4.3 (1.20)
P-value[e] for difference from MorCAP		**0.0129**	**0.0013**		**0.0407**	**0.0347**
uKS (%)						
N	72	51	160	23	47	142
LS mean change from baseline[c] (SE)[d]	32.7 (7.64)	-57.6 (9.06)	-56.8 (5.16)	5.6 (6.98)	-63.8 (6.60)	-60.9 (3.77)
P-value[e] for difference from MorCAP		<**0.0001**	<**0.0001**		<**0.0001**	<**0.0001**
MPP Population/MorCAP 2						
6MWT (m)						
N	67	43	123	27	41	117
LS mean change from baseline[c] (SE)[d]	-6.7 (8.78)	38.5 (11.02)	38.4 (6.47)	-21.9 (12.30)	39.0 (11.32)	32.9 (6.66)
P-value[e] for difference from MorCAP		**0.0016**	<**0.0001**		**0.0003**	**0.0001**
3MSCT (stairs/min)						
N	67	43	123	27	41	117
LS mean change from baseline[c] (SE)[d]	0.5 (1.51)	5.5 (1.85)	6.9 (1.08)	-1.2 (2.39)	6.2 (2.24)	6.9 (1.32)
P-value[e] for difference from MorCAP		**0.0375**	**0.0007**		**0.0236**	**0.0033**
uKS (%)						
N	59	41	118	13	38	108
LS mean change from baseline[c] (SE)[d]	29.6 (9.30)	-57.5 (11.16)	-56.4 (6.59)	6.2 (8.46)	-63.8 (7.47)	-62.8 (4.41)
P-value[e] for difference from MorCAP		<**0.0001**	<**0.0001**		<**0.0001**	<**0.0001**

LS: least square; SE: standard error.
[a] Year 1 represents data collected from the MOR-004/005 Week 72 assessment and the MorCAP Year 1 follow-up window.
[b] Year 2 represents data collected from the MOR-004/005 Week 120 assessment and the MorCAP Year 2 follow-up.
[c] Baseline LS means are based on ANCOVA of baseline measurement with model terms treatment age group, and 6MWT distance category.
[d] LS mean changes based on repeated measures ANCOVA model including treatment, time point, treatment and time point interaction, age group, and baseline 6MWT category, and baseline measurement (3MSCT and uKS only).
[e] *P*-value determined by *t*-test and the repeated measures ANCOVA model.

distances than those who did not; both groups maintained their initial improvements throughout the study (Appendix Fig. B2). Age was also evaluated and no clear impact on 6MWT results was detected (Appendix Fig. B3).

3.3. Secondary efficacy measures

3.3.1. 3MSCT

Mean (SE) changes from pre-treatment baseline in the 3MSCT for the QW-QW cohort were 4.6 (1.1), 5.9 (1.1), 5.0 (1.4), and 5.5 (1.9) stairs/min and 3.9 (1.2), 5.5 (1.3), 5.7 (1.5), and 6.7 (2.0) stairs/min at 24, 36, 72, and 120 weeks in the ITT (Fig. 4A) and MPP (Fig. 4B) populations, respectively. Mean (SE) changes in the 3MSCT for all cohorts pooled were 4.8 (1.2), 5.0 (0.8), 5.2 (1.0), and 4.3 (1.2) stairs/min and 4.4 (0.8), 5.5 (0.9), 7.0 (1.1), 6.8 (1.3) stairs/min at 24, 36, 72, and 120 weeks in the ITT and MPP populations, respectively (Fig. 4C). Assuming similar timing of approximately 1 and 2 years follow-up in MorCAP and MOR-004/005, model-based ANCOVA analysis demonstrates a significant difference in change from baseline for treated versus untreated patients, for both ITT and MPP populations in the QW-QW cohort and all cohorts pooled (Fig. 5, Table 2).

3.3.2. Normalized uKS

Unlike endurance measures, normalized uKS is not influenced by factors such as joint abnormalities, neurological problems, patient motivation, or orthopedic surgeries. Response to treatment is, therefore, more robust, allowing for interpretation of the uKS results by individual treatment cohort. The rapid decline in normalized uKS seen in MOR-004 in patients on elosulfase alfa treatment [8] was followed by a continuous gradual decline in MOR-005 (Fig. 6). In patients who switched from placebo to elosulfase alfa at the beginning of MOR-005, a rapid initial decline in uKS was observed. Patients receiving elosulfase every other week during part 1 of the study experienced slower declines in uKS than those receiving weekly treatment. Cohorts receiving every other week treatment showed a further gradual decline in uKS when transitioned to weekly doses, further supporting the finding from the pivotal study [8] that weekly treatment is necessary for optimal effect. Reductions in uKS were seen regardless of age cohort (data not shown). By Week 120, when all patients were receiving weekly treatment, the mean percent change from baseline was similar for all cohorts. Mean (SE) change in normalized uKS was −59.4 (1.8)% in the pooled ITT population and −62.3 (1.8)% in the pooled MPP population. These changes resulted in mean 120 week uKS levels of 10.2 and 8.5 μg/mg creatinine in the pooled ITT and MPP populations, respectively.

Assuming similar timing of approximately 1 and 2 years follow-up in MorCAP and MOR-004/005, model-based ANCOVA analysis demonstrates a highly significant ($P < 0.0001$) difference in change from baseline for treated versus untreated patients, for both the QW-QW cohort and the pooled study population (ITT and MPP) (Table 2).

3.4. Safety

Table 3 summarizes AEs and serious AEs (SAEs) reported for all patients (ITT population) during MOR-005 by treatment cohort. No new or unexpected safety signals were identified since the original publication. The safety profile was consistent with that observed in MOR-004 and the post-marketing setting to date.

The most commonly reported AEs overall were mild to moderate IARs such as vomiting, pyrexia, and headache, which were generally manageable with symptomatic treatment and/or infusion rate modification. While all patients reported at least one AE during the study,

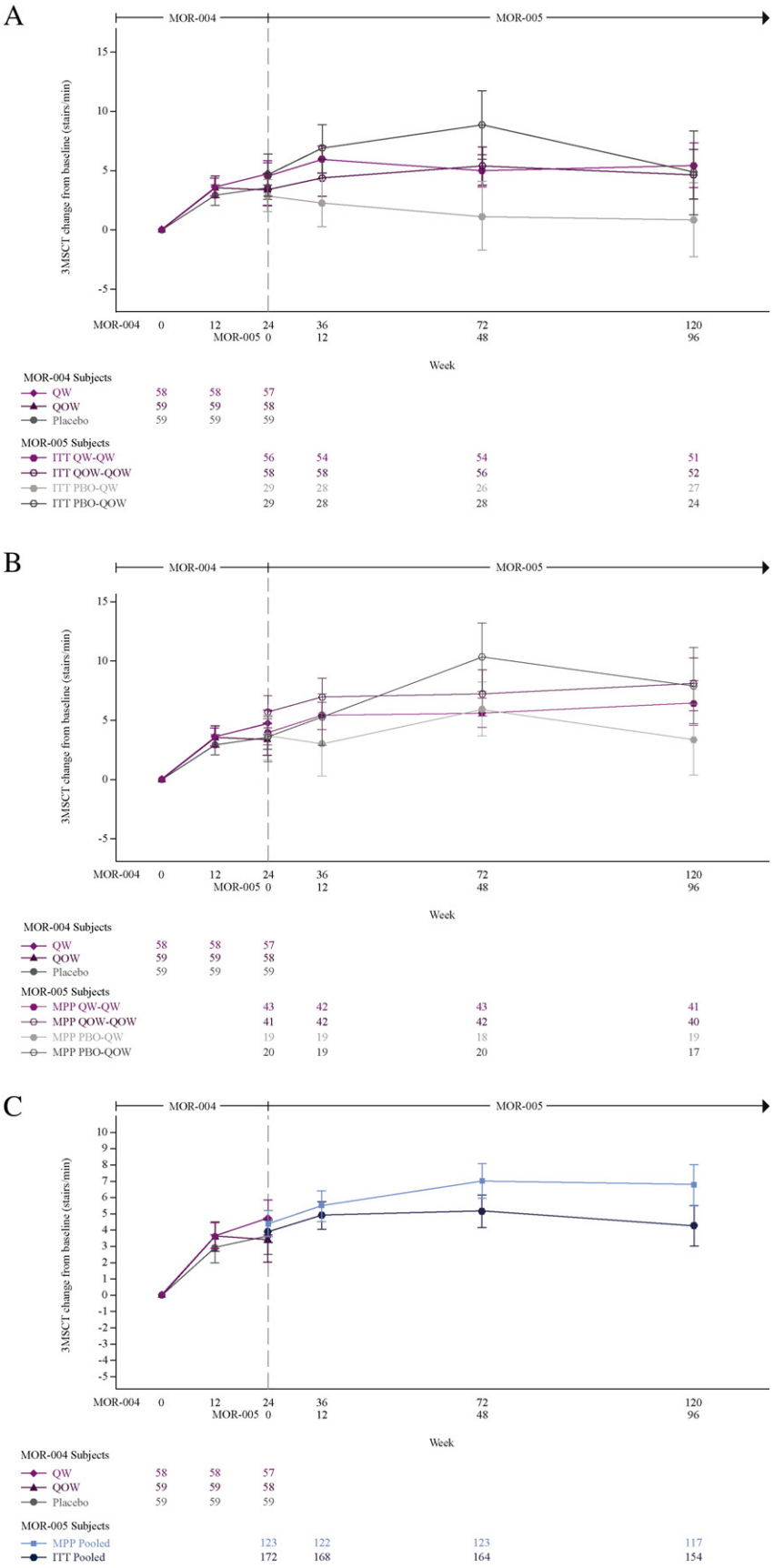

Fig. 4. Mean (SE) change from baseline in 3MSCT results over 120 weeks for treatment cohorts individually (A, B) and pooled (C) for ITT and MPP populations. The number of patients with data available are shown below each time point.

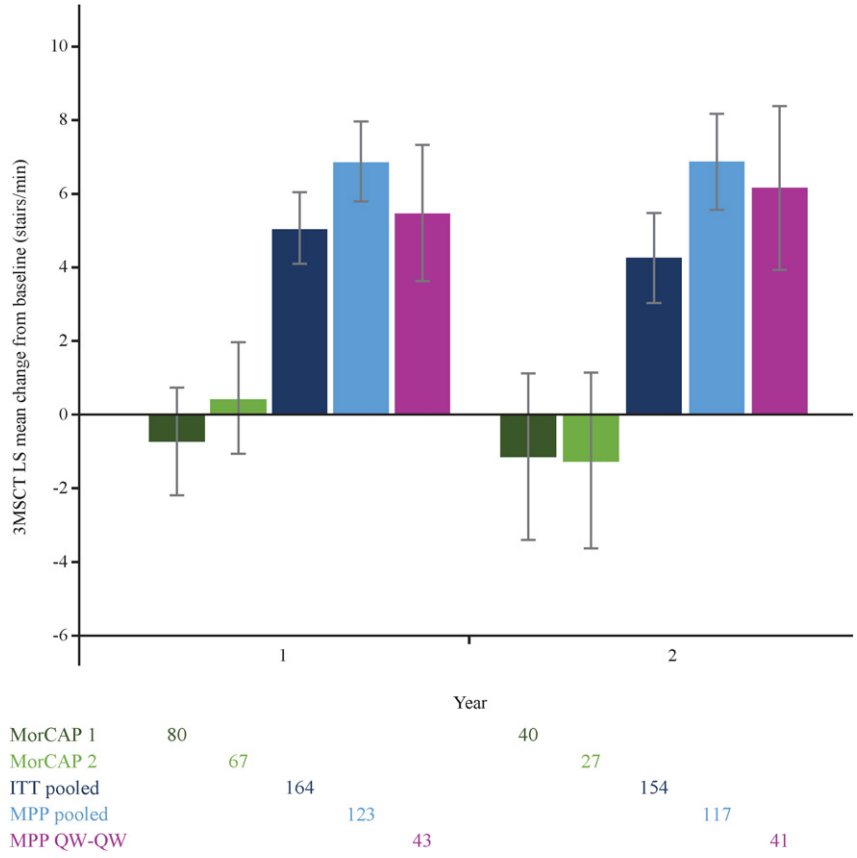

Fig. 5. LS mean 3MSCT changes from baseline (stairs/min) over approximately 2 years in MOR-004/005 QW-QW and pooled ITT and MPP populations and the corresponding untreated subpopulations from the MorCAP natural history study, MorCAP 1 and 2, respectively. The number of patients with data available are shown below each time point. LS mean changes are based on repeated measures ANCOVA model including treatment, time point, treatment and time point interaction, age group, baseline 6MWT category, and baseline measurement.

<3% of patients permanently discontinued the study drug. Of the 15,141 infusions administered, 81 (0.5%) were interrupted or discontinued because of an AE requiring medical intervention.

Most SAEs occurring during MOR-005 were related to planned surgical procedures, which were allowed in MOR-005, but not in MOR-004. There were two study-drug related SAEs which occurred in separate patients, anaphylaxis (grade 4) and hematuria (grade 2). One death unrelated to elosulfase alfa occurred due to postoperative pulmonary complications secondary to spinal cord compression, laminectomy, and spinal fusion.

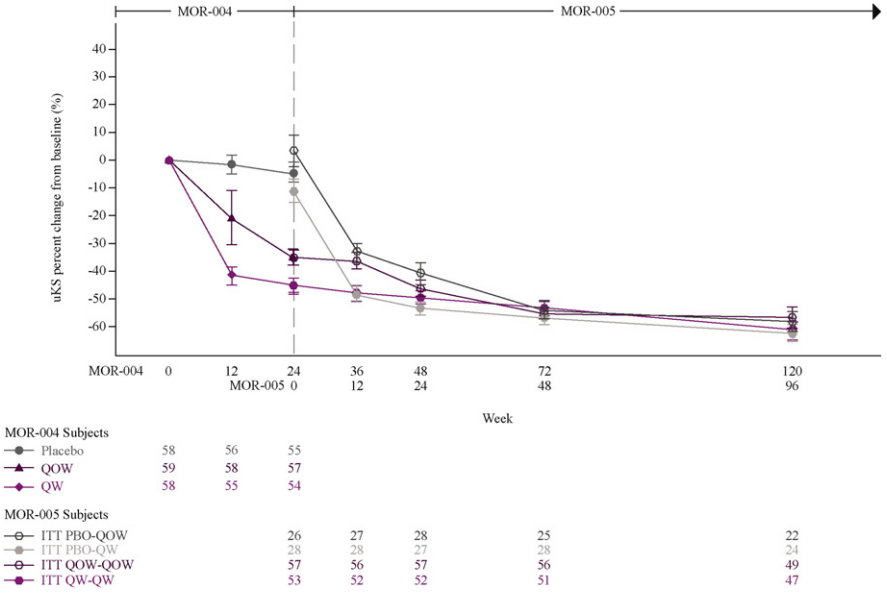

Fig. 6. Percentage mean (SE) change from baseline in normalized uKS over 120 weeks for individual treatment cohorts from ITT population. The number of patients with data available are shown below each time point.

Table 3
Overall summary of adverse events during MOR-005 (ITT population).

	PBO-QOW ($N = 29$)	PBO-QW ($N = 29$)	QOW-QOW ($N = 59$)	QW-QW ($N = 56$)
Any AE, N (%)	29 (100.0%)	29 (100.0%)	59 (100.0%)	56 (100.0%)
Number of AEs per patient, N				
Mean	39.9	24.9	30.8	35.9
Median	30.0	18.0	24.0	26.5
Any study drug-related AE, N (%)	23 (79.3%)	20 (69.0%)	40 (67.8%)	43 (76.8%)
Any SAE, N (%)	16 (55.2%)	14 (48.3%)	24 (40.7%)	23 (41.1%)
Number of SAEs per subject, N				
Mean	0.8	0.7	0.7	0.7
Median	1.0	0.0	0.0	0.0
Any study drug-related SAE, N (%)	2 (6.9%)	0 (0%)	0 (0%)	0 (0%)
Any AE leading to permanent study drug discontinuation, N (%)	0 (0%)	0 (0%)	3 (5.1%)	1 (1.8%)
Death, N (%)	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)

AE: adverse event; SAE: serious adverse event.

All patients treated with elosulfase alfa developed anti-drug antibodies, and nearly all developed NAb (antibodies capable of interfering with CI-M6PR binding in vitro). At Week 120, 100% of patients were positive for total antibody (TAb) directed against elosulfase alfa (Fig. 7a), and a majority were positive for NAb. No association was detected between higher TAb titer or NAb positivity and reduced efficacy measurements (6MWT, 3MSCT, and uKS) (Fig. 7b-d) or the incidence or severity of hypersensitivity AEs. Drug-specific IgE was detected in 17/176 (9.7%) subjects in the ITT population by Week 120, and positivity was not consistently associated with the occurrence of anaphylaxis, other hypersensitivity AEs, and/or treatment withdrawal.

4. Discussion

Initial improvements in endurance and reductions in uKS reported in the elosulfase alfa pivotal study [8] were sustained in this extension study over a total of 120 weeks. For patients treated with elosulfase alfa at 2.0 mg/kg/week throughout the study, mean 6MWT improvements from baseline were 32.0 and 39.9 m for the ITT and MPP populations, respectively, as compared to the 22.5 m improvement reported in the pivotal study [8]. Although the minimal clinically important difference (MCID) in the 6MWT has not yet been identified for Morquio A patients, it was noted in the pivotal study publication that the level of improvement seen with elosulfase alfa falls within the spectrum of 6MWT MCIDs identified for other disorders [8].

Sustained improvements of 5.5 and 6.7 stairs/min in the 3MSCT at 120 weeks for the weekly treatment cohort (ITT and MPP populations, respectively) corroborated the 6MWT findings, as did sustained reductions in uKS. Interestingly, uKS levels continued to decline gradually, even after 72 weeks, suggesting possible continued depletion of stored glycosaminoglycan with long-term treatment. Alternatively, the gradual decline seen may be a result of the decline in uKS levels that occurs with age, or a combination of both factors.

Interpretation of results from this extension study was complicated by several factors, including the staggered transition to the weekly dosing regimen, occurrence of orthopedic surgeries among the patients, and absence of a placebo group. While transitioning all patients to QW dosing of elosulfase alfa at the time the optimal treatment regimen was identified contributed to the complexity of the study, the decision to do so was deemed to be in the best interest of the patients.

Due to the severe skeletal involvement of Morquio A patients and the importance of surgical management of symptoms, orthopedic surgeries could not be delayed for the duration of the extension study. Endurance test results may have been compromised by the orthopedic surgeries and subsequent recovery periods for 38 of the 173 patients. Alternatively, potential improvements resulting from surgical interventions could also bias the results. Therefore, these patients were excluded from the MPP population. Excluding patients undergoing orthopedic surgery during the study had the potential to bias the results if those patients were more severely affected. However, ITT and MPP populations had similar baseline 3MSCT and uKS means and the MPP population had a lower 6MWT mean than the ITT population (201.6 versus 209.5 m). Therefore, in this study, the need for orthopedic surgery does not appear to have been indicative of severity of endurance limitation or uKS levels.

A placebo group was not included as continuing invasive weekly infusions in the absence of treatment for the duration of this long-term extension study was considered unethical. In the absence of a placebo group, a direct evaluation of treatment efficacy could not be made. However, data from untreated patients, available from the MorCAP natural history study, were used to place the results of this study in the context of a progressive disease. The main limitations to these comparisons were the decreasing number of observations available for analysis at later time points of the MorCAP study and the potential for differences between the MOR-004/005 and MorCAP populations and study executions. The fact that some (exact number could not be determined from available data) MorCAP patients subsequently enrolled in MOR-004/005 and are, therefore, providing data to both populations, should also be noted.

To establish the untreated population to be used for comparison, MorCAP patients were evaluated by the inclusion and exclusion criteria for MOR-004/005 to the extent possible. The MPP population excluded patients who were non-compliant as determined by missed infusions equaling or exceeding 20%, however, as MorCAP patients were untreated, these criteria could not be applied. Ultimately, comparison of MorCAP 2 and MPP population baseline data reveal similar endurance results, although uKS is slightly higher in the MorCAP 2 population.

When compared to the corresponding MorCAP subpopulations, MOR-005 ITT and MPP populations' 6MWT and uKS results demonstrated sustained treatment effects at both 1 and 2 years ($P < 0.05$). These effects are greater if only patients receiving the optimal dose for 120 weeks are considered. For 3MSCT results, which did not reach significance during MOR-004, statistical significance was achieved over the long-term MOR-005 study, in both the ITT and MPP populations, at 1 and 2 years versus the MorCAP subpopulation ($P < 0.05$). The more gradual course of 3MSCT improvement, as compared to 6MWT improvement, is noteworthy and may indicate that the 3MSCT is less sensitive to shorter term treatment effects than the 6MWT in Morquio A patients. This may be due to the increased challenge stair-climbing poses for Morquio A patients in comparison to walking in the 6MWT, due to extremely short stature and disease involvement of the ankles, knees, and hips, as well as the upper extremities which aid in stair climbing via the hand rail.

A significant correlation has recently been reported between clinical 6MWT and 3MSCT outcomes and patient-reported quality of life outcomes [12]. Results from a Morquio A patient-reported outcomes survey indicated that quality of life is mainly dependent upon the patient's ability to remain independently mobile and that even slight improvements in mobility dramatically improve quality of life [5]. The

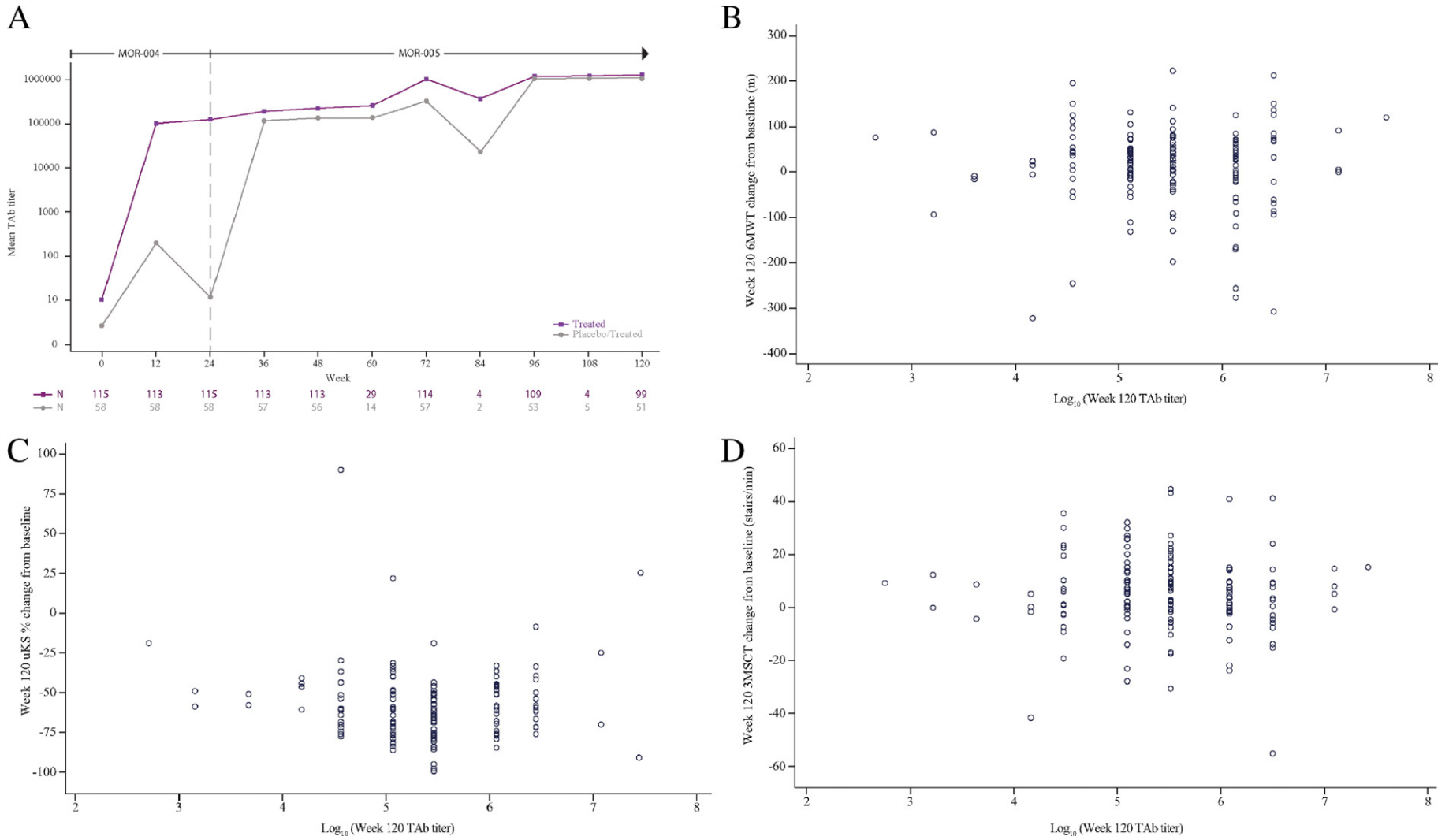

Fig. 7. TAb titer of patients in the ITT population (A) over time in those receiving treatment during MOR-004 and MOR-005 (treated) and those receiving placebo during MOR-004 and treatment during MOR-005 (placebo/treated); (B–D) at Week 120 versus Week 120 6MWT and 3MSCT change from baseline, and uKS percent change from baseline.

long-term, sustained improvements in endurance reported in this study may well enable patients to decrease their dependence on a wheelchair, increasing their mobility and independence, lessening caregiver burden, and improving their quality of life.

5. Conclusions

In the context of a chronic progressive disease, elosulfase alfa ERT led to improvements in endurance which were sustained over 120 weeks. Improvement and subsequent stabilization seen in 6MWT and 3MSCT results significantly differed from the gradual decline seen in corresponding subpopulations of untreated patients from the MorCAP natural history study. Initial endurance improvements were maintained regardless of the endurance capacity of patients at baseline, use of a walking aid, and age. Long-term treatment resulted in sustained reduction of uKS levels. The development of anti-drug antibodies had no apparent impact on long-term endurance outcomes or uKS levels and no impact on long-term drug safety/tolerability. No new or unexpected safety signals were identified. Ultimately, the benefits of elosulfase alfa ERT are enduring and appear to substantially alter the expected course of disease for Morquio A patients.

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Appendix A. Supplementary data

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